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Review

Management of uveal tract melanoma: A comprehensive review

Akhil Kapoor [a,*], **Vimla Beniwal** [b], **Surender Beniwal** [c], **Harsh Mathur** [d], **Harvindra Singh Kumar** [a]

[a] *Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment & Research Institute, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Rajasthan, India*
[b] *Department of Opthalmology, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Rajasthan, India*
[c] *Department of Medical Oncology, Acharya Tulsi Regional Cancer Treatment & Research Institute, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Rajasthan, India*
[d] *Department of Opthalmology, Moti Lal Nehru Medical College and Associated Group of Hospitals, Allahabad, Uttar Pradesh, India*

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Abstract Uveal tract melanoma is the most common primary intraocular malignancy in adults, accounting for about 5–10% of all the melanomas. Since there are no lymphatic vessels in the eye, uveal melanoma can only spread hematogenously leading to liver metastasis. A wide variety of treatment modalities are available for its management, leading to dilemma in selecting the appropriate therapy. This article reviews the diagnostic and therapeutic modalities available and thus, can help to individualize the treatment plan for each patient.

Contents

* Corresponding author at: Room No. 73, PG Boys Hostel, PBM Hospital, Bikaner, Rajasthan 334003, India. Mobile: +91 9950482121.
E-mail address: kapoorakhil1987@gmail.com (A. Kapoor).

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Introduction

Uveal tract melanoma (UVM) is the most common primary intraocular malignancy in adults, accounting for about 5–10% of all the melanomas [1]. Male: female ratio is 1.3:1. The disease is rare in children and young adults, the incidence rises gradually with age peaking at about 70 years [2]. In the famous Collaborative Ocular Melanoma Study (COMS), the risk of distant metastasis at 10 years of diagnosis was 34% [1]. Also, after the diagnosis of metastasis, the median time to death was six months [3]. Several risk factors for melanoma have been identified including fair skin, having blond or red hair, light-colored eyes, extensive freckling, history of one or more severe, blistering sunburns, excessive ultraviolet (UV) light exposure, living closer to the equator or at a higher elevation, having >50 mol or atypical moles (dysplastic nevi), a family history of melanoma and immunosuppression [4].

The uveal tract comprises of iris, ciliary body, and choroid, and UVM can involve one or more structures. Ciliary body and choroidal melanomas constitute about 95% of all UVM. Iris is reported to harboring melanoma in only 5% of cases. Another distinguishing peculiarity of iris melanoma is that it very rarely metastasises [5].

Melanoma is named so because of its origin from melanocytes. However, the amount of pigment in the lesion varies giving rise to a spectrum of color usually dark brown and black. There have been reports of amelanotic melanoma in various parts of the body [6]. Recent studies suggest a relationship between tumor pigmentation and risk of growth and metastasis, with a better prognosis for lightly pigmented or amelanotic lesions [7]. A typical choroidal melanoma is dark brown and elevated subretinal mass. In 1931, Callender documented distinctive cell types in the gamut of cells composing UVM. The modified Callender classification is based on cell size, shape, cytoplasmic features, loss of cohesion, nuclear and nucleolar characteristics. Three categories according to this system include spindle cell melanomas (30% of intraocular tumors), mixed-cell melanomas (65%), when fewer than half of the cells in the sections examined are composed of epithelioid cells, and epithelioid cell melanomas, when greater than half of the tumor sections are composed of epithelioid cells, accounting for 5% of UVM [8]. The pathologist's designation of a particular cell type involves subjective judgment.

UVM usually remains confined to the globe. Larger tumors may develop extra-scleral extension, with approximately 15% of cases demonstrating extra-scleral extension. Other pathways of extraocular spread include the optic nerve and the lumen of vortex veins [9]. Since there are no lymphatic vessels in the globe, UVM can only spread hematogenously. Distant metastasis is identified in almost 50% of patients after 25 years of diagnosis [10]. Liver is the most common (89%) site of distant metastasis [11].

Diagnosis

Clinical examination

The diagnosis of UVM is frequently clinical, with accuracy reaching 99.7% in specialized centers [12].

Ultrasonography

The combined use of A- and B-mode techniques is vital in confirming the clinical diagnosis of choroidal melanoma with

an accuracy of >95% [13]. On A-scan ultrasonography, choroidal melanoma shows medium to low internal echoes with smooth attenuation along with vascular pulsations within the tumor. On B-scan, there are three classic features of choroidal melanoma: an acoustically silent zone within the tumor, choroidal excavation and shadowing in the orbit [14]. Besides, ultrasonography acts as a valuable tool for follow up in patients with conservative treatment.

Photography

Fluorescein angiography is highly useful in differentiating melanoma from hemorrhage or hemangioma. In patients with melanoma, it usually causes irregular hyperfluorescence in the early phase while staining of the tumor is observed in the late phase [15]. However, the orange pigmentation in the retinal pigment epithelium typically blocks the early hyperfluorescence. Larger melanomas may show a patchy pattern of early hypofluorescence and hyperfluorescence followed by late intense staining. Some choroidal melanomas demonstrate intrinsic vascularization, visible throughout the angiogram. The angiographic sign, called the "double circulation pattern," refers to simultaneous fluorescence of retinal and choroidal circulation within the tumor. When it occurs, it is fairly distinctive of choroidal melanomas [15]. Also, very important roles of colored fundus photographs are the accurate assessment and follow up of the basal dimension of the lesion primarily and post treatment.

The patterns of indocyanine green videoangiography (ICGV) are variable, depending primarily on the degree of tumor pigmentation, thickness, and vascularity. In the early frames of ICGV, hypofluorescence can be observed in all cases [14]. Intrinsic choroidal vasculature is discernible in some cases. In the late phase of ICGV, the patterns include hyperfluorescence and three-ring [15].

Fine-needle aspiration biopsy (FNAB)

Obtaining the pathology report prior to starting definitive treatment is not routinely recommended. However, when the clinical diagnosis is uncertain, then diagnostic biopsy can be considered balancing the potential risks of the procedure. FNAB can be performed either with a direct transscleral or transvitreal approach. Prognostic biopsy is also considered, if the patient desires for it. The current practice now in the most advanced centers in the world dealing with uveal melanomas is to obtain FNAB for cytogenetic studies of the tumor at the time of treatment (plaque or enucleation) and in the few cases where there is doubt about the clinical diagnosis.

Other diagnostic tools

Ocular coherence tomography (OCT) is a useful adjunct to differentiate large choroidal nevi from melanomas [14]. Choroidal nevi tend to have clearly defined margins and to be flat or slightly elevated, and they remain stable in size. In contrast, choroidal melanomas are more likely to show signs of activity such as relatively indiscrete margins, irregular or oblong configuration, overlying subretinal fluid and orange pigment, and abruptly elevated edges.

Magnetic resonance imaging (MRI) can be used to provide intraocular enhancement of the lesion that may help in predicting the degree of malignancy and for monitoring the response to treatment.

Metastatic workup

Since melanoma has a high risk of distant metastasis, thorough physical examination, imaging studies and biochemical tests are necessary as the baseline work up. Abdominal ultrasonography, chest X-ray, and computed tomography (CT) of the head are useful in the staging work up. The results of COMS study indicate that liver function tests, followed by diagnostic tests, are highly specific and have high predictive values but the sensitivity remains low [16]. Some institutions employ whole-body positron emission tomography/CT as a part of staging work up [17]. The presence of tyrosinase or *MelanA/MART1* transcripts have been reported to be an independent prognostic factor for the development of metastases [18,19].

Staging

Staging is an important tool in the prognostication of the patient but it should not delay the primary management of the tumor. Patients should have whole body staging (chest, abdomen and pelvis) with CT scan or PET-CT. Brain imaging and bone scan are required only in presence of related symptoms. In patients with liver metastasis, in order to assess for resectability, contrast enhanced MRI with diffusion weight imaging is required. For extra hepatic disease, contrast-enhanced CT scan is advisable for accurate staging. COMS staging is widely used, it takes into account tumor thickness and basal diameter [20]. The results of various randomized clinical studies are based on COMS staging. The current TNM staging by the American Joint Committee on Cancer (AJCC) draws somewhat different boundary lines for small, medium, and large tumors [21].

Management

The therapy selected for choroidal melanoma should be individualized and is dependent on various factors, such as patient's age, tumor size and location, general health, and status of the fellow eye. However, there is no proven survival advantage between any of the offered modalities.

Small choroidal melanoma

In the management of suspected small choroidal melanomas, the most important issue is to decide when to start definite therapy. The authors recommend each case to be individualized. The useful therapies include transpupillary thermal therapy (TTT) and radiation therapy [22]. Besides, plaque radiotherapy can also be used by an experienced clinician to treat small uveal melanomas [23]. There exists a controversy about treatment of certain uveal melanomas. For example, in the diagnosis of "small" AJCC T1 uveal melanomas, the American Brachytherapy Society (ABS)-Ophthalmic Oncology Task Force (OOTF) recommends that in the absence of thickness $\geqslant 2$ mm, subretinal exudative fluid and superficial orange pigment lipofuscin tumors; patients could be offered the alternative of "observation" for the evidence of change (within 6 months) typically for documented growth prior to intervention. This is particularly applicable for tumors near the fovea and optic nerve, or monocular patients where treatment is likely to cause radiation related vision morbidity.

Table 1 Table showing treatment options according to size of ocular melanoma.

Feature		Small choroidal melanoma	Medium choroidal melanoma	Large choroidal melanoma
Criteria for size	Apical height Largest basal diameter	1–2.5 mm 5 mm	2.5–10 mm 5–16 mm	> 10 mm > 16 mm
Treatment options		• Laser photocoagulation • Transpupillary thermal therapy (TTT)	• Plaque radiotherapy • Proton beam therapy • Stereotactic radio surgery (SRS)	• Customized plaque RT • Enucleation

Laser photocoagulation therapy

Xenon arc photocoagulation was replaced by argon laser photocoagulation, which showed fewer complications but less tumor control [24]. The major limitations of laser therapy include poor tissue penetration and the requirement for multiple treatment sessions. Hence, laser therapy has been superseded by TTT.

Transpupillary thermal therapy

Infrared light (diode laser, 810 mm) is used as heat to induce necrosis in tumor tissues. The tumor recurrence rate was 10% at 3 years, with visual acuity worse than 20/200 in 32% of cases in the report by Shields et al. [23]. The ideal candidate for TTT is small, heavily pigmented melanoma less than 3 mm thick with minimal or no subretinal fluid, located in the extramacular region but not touching the optic disk. Delayed recurrence and extrascleral extension are the important drawbacks of TTT. This treatment can be used as an adjunct to plaque radiotherapy [22].

Medium-sized choroidal melanoma

Plaque radiotherapy results in equivalent survival as that of enucleation for the management of medium sized choroidal melanoma [25]. Local sclero-chorioretinal resection can reserve vision with good cosmesis [26]. However, it is associated with early complications leading to preference for radiotherapy for this indication (see Table 1).

Radiation therapy

Radiotherapy is presently the most widely used treatment for medium-sized posterior uveal melanoma [27]. The armamentarium of radiation therapy for melanoma includes plaque brachytherapy, external-beam radiation using photons or charged particles (protons and helium ions) and stereotactic radiosurgery with modified linear accelerators and multisource cobalt units [28–30]. A comparison of these techniques is given in Table 2.

Episcleral plaque radiation therapy

ABS-OOTF recommends that brachytherapy exclusion criteria include: tumors with gross (T4e or > 5 mm) extraocular extension, blind painful eyes and those with no light perception vision [31].

The custom-designed plaque is temporarily sutured to the sclera overlying the tumor, usually under retrobulbar or general anesthesia. Operative localization of the plaque placement is guided by translumination, ophthalmoscopic observation, or ultrasonography. The plaque remains in place for 2–5 days, depending on the type and activity of the radioactive source, and it is then removed under similar operative conditions.

Iodine 125 (^{125}I) is the most commonly used radioisotope [32]. Ruthenium 106 (^{106}Ru) is frequently used in Europe; other isotopes include cobalt 60 (^{60}Co) and palladium 103 (^{103}Pd) [33]. Isotopes with lower photon and electron radiation (^{125}I, ^{106}Ru, ^{103}Pd) are more easily shielded to reduce the exposure to adjacent normal tissues in the patient, with a concomitant reduction in exposure risk to medical personnel. The radioisotope ^{103}Pd has dosimetric advantages based on its lower photon energy as compared to ^{125}I. Clinical trials of ^{103}Pd have been favorable [34].

Charged-particle beam therapy

Charged-particle beams (protons or helium ions) are available at a relatively few sites around the world. These have dosimetric advantage in terms of delivery of a high dose of radiation to highly precise targets. A retrospective review of 218 patients treated with helium ion irradiation, with a minimum follow-up period of 10 years, demonstrated 95% local control [28]. Twenty-two percent of patients required enucleation, most often for anterior segment complications. Impairment of visual acuity was noted for tumors $\geqslant$6 mm thick and located within 3 mm of the optic nerve and fovea [32].

A large single-institution retrospective comparison of proton beam-treated patients with those undergoing enucleation showed no apparent difference in long-term survival: an update on 1922 patients with a median follow-up of 5.2 years showed 5- and 10-year local failure rates of 3.2% and 4.3%, respectively, following proton beam radiation (PBR) [29]. Approximately half of the failures were marginal, suggesting possible treatment planning or delivery errors. Another survival study on the relative rates of metastatic death, cancer death, and all-cause mortality between enucleation and PBR revealed a statistically significant survival benefit in the PBR group in the first two years of treatment. However, by the sixth year the survival benefit was not maintained. In general, it appears that tumor control with charged-particle and plaque radiotherapy, as well as radiation complications, is similar.

One early main complication after PBR is intraocular inflammation. Lumbroso et al. found 28% of patients developed ocular inflammation [35]. It is correlated with larger

Table 2 Table showing review of all the available treatment options for ocular melanoma.

Treatment	Used for	Outcomes	Complications	Comments
Radiotherapy				
Brachytherapy ruthenium[106] Iodine[125]	Small/medium /large uveal melanoma* <20 mm in basal diameter	Good local tumor control	Loss of vision tumor recurrence	Dose and position of plaque can be adjusted to limit the loss of vision
Proton Beam radiotherapy	Medium to large uveal melanoma which cannot be treated with brachytherapy or resection	Good local tumor control	Loss of vision Loss of the eye from neovascular glaucoma tumor recurrence	Not available in all ocular oncology units
Stereotactic radiosurgery	Juxta-papillary uveal melanoma; patients unsuitable for ruthenium plaque or unfit for surgery	Good local tumor control	Loss of vision Radiation related complications tumor recurrence	Lower availability
Phototherapy				
Transpupillary thermotherapy	Local recurrence and of adjuvant therapy of uveal melanoma	Improves local tumor control	Loss of vision Extraocular tumor recurrence	Very occasionally used by some centers for small melanoma nasal to the optic disk. When considering preservation of vision, for example in a one eyed patient; as it avoids radiotherapy complications. However, it is no longer recommended routinely as a sole primary treatment.
Photodynamic therapy	Small melanoma	Uncertain	Tumor recurrence	Avoids radiotherapy complications New treatment option not widely used for uveal melanoma. This is an experimental treatment.
Surgery				
Exoresection +/− plaque	Medium to large melanoma with a narrow basal diameter	Variable	Retinal detachment Loss of vision Loss of the eye tumor recurrence Risk of orbital dissemination of tumor	Rarely performed Always performed with brachytherapy to reduce the risk of recurrence
Endoresection +/− radiotherapy	Medium-sized uveal melanoma Toxic tumor syndrome post PBR	Variable	Transient intraocular haemorrhage; rarely tumor seeding	Only performed in limited centers
Enucleation	Large uveal melanoma Melanoma associated with NVG +/− extensive retinal detachment	100% local tumor control if completely excised	Socket related complications Orbital recurrence	Cosmetic results are reasonably good with an orbital implant and artificial eye
Exenteration	Large extra-ocular extension after uveal melanoma	100% local tumor control if completely excised	Orbital recurrence	Rarely performed

Table 3 Modalities for surveillance of uveal melanoma: advantages and disadvantages.

Modality	Advantages	Disadvantages
Liver function tests	High NPV, inexpensive, accessible	Low sensitivity, poor PPV
Chest X-ray	Noninvasive, inexpensive, accessible	Low sensitivity, low yield
Abdominal Ultrasonography	Noninvasive, inexpensive, accessible	Limited by body habitus, operator dependent
Computed Tomography	High sensitivity, whole body imaging, moderate/high resolution	Low PPV, false positives, radiation exposure
PET/CT	Whole body imaging	Lower specificity, expensive, inaccessible, poor resolution, UM moderately FDG avid, radiation exposure, false positives
Magnetic Resonance Imaging	High resolution/sensitivity, good detection for lesions >1 cm	Limited by body habitus, metallic implant and claustrophobia, false positives

NPV, negative predictive value; PPV, positive predictive value; UM, uveal melanoma; FDG, fludeoxyglucose (^{18}F).

initial tumors (tumor height and irradiation of a large volume of the eye) and may be related to an exudative retinal detachment and tumor necrosis, both of which in turn are thought to lead to an associated release of cytokines and neovascular glaucoma (termed, 'toxic tumor syndrome').

Large choroidal melanoma

Enucleation is generally reserved now for advanced melanomas greater than 15 mm in diameter and more than 10 mm thick. It is also employed with the resection of a long portion of optic nerve in cases where there is optic nerve invasion. Plaque radiotherapy can also be customized to treat large uveal melanomas [34]. Patients with large tumors or with tumors at peripapillary and macular locations have a poorer visual outcome and lower local control that must be taken into account in the patient decision-making process.

Orbital exenteration

Orbital exenteration was previously done in every case of extrascleral extension. However, it does not significantly improve survival for patients with mild to moderate extrascleral extension [36]. In cases of massive orbital extension occurring with a blind, painful eye, primary orbital exenteration appears justified.

Pre-enucleation external beam radiation

Pre-enucleation radiotherapy for uveal melanoma was thought to possibly reduce enucleation-induced systemic metastasis. However, a randomized trial by COMS involving 1000 patients failed to show any survival advantage by pre-enucleation radiation [37].

Management of patients with metastatic disease

The prime route of spread of ocular melanoma is hematogenous, with liver being the most common site of distant metastasis. In the COMS study, the sites of metastases at death were liver in 91%, lung in 26%, bone in 18%, skin in 12%, and lymph nodes in 11% of patients [20]. Hepatic metastases are recognized as a poor prognostic marker for response to treatment and survival. The overall 1-year survival after the development of metastasis is only 13%, and median survival estimates range from 2 to 9 months [21]. Surgical resection of liver metastases not indicated as melanoma is a systemic disease at this stage. The ABS-OOTF recommends that the presence of metastatic disease from uveal melanoma is not an absolute contraindication for brachytherapy. For example, there exist ocular situations where brachytherapy may limit or prevent vision loss from tumor associated retinal detachment or when tumor growth will soon cause secondary angle closure glaucoma. In addition, brachytherapy of the primary tumor may allow the patient to enter systemic treatment trial where a small proportion will survive. Systemic chemotherapy has been ineffective, with response rates reported to be 1% or less in most series, and cytokine therapy with interleukin-2 and interferon-γ have been similarly ineffective [38]. A variety of regional treatment modalities, such as hepatic arterial chemotherapy, hepatic artery chemoembolization, regional immunotherapy, isolated hepatic perfusion, and percutaneous hepatic perfusion, are being used to control tumor progression in the liver. Most reports show at best a modest response rate, suggesting that selected patients with uveal melanoma may occasionally benefit from aggressive treatment. In the absence of a proven standard of care or clinical trial, many patients with metastatic uveal melanoma currently receive best supportive care or dacarbazine chemotherapy for 4–6 cycles. Unlike skin melanoma, mutations in the BRAF gene are exceptionally rare and thus for these patients BRAF-directed therapies are unhelpful [39].

The anti-CTLA4 agent, ipilimumab has National Institute for Health and Care Excellence (NICE) approval for previously treated advanced (unresectable or metastatic) melanoma based upon clinical trials in skin melanoma. There are two independent, favorable prognostic factors: fewer than ten metastases at screening and the absence of ciliary body involvement. The increasing understanding of the underlying biology of uveal melanoma has led to the identification of a number of novel and promising therapeutic strategies that warrant investigation. Currently, an increasing number of novel agents are under evaluation in well-designed prospective and uveal-specific phase II clinical trials. A randomized phase II study in 98 patients compared selumetinib versus temozolomide has reported improved response rate and doubling of PFS (15.9 versus 7 weeks) [40]. Pembrolizumab (MK-3475) is a drug that targets the programed cell death 1 (PD-1) receptor meant to treat metastatic melanoma [41]. As per an abstract presented in recent ASCO meeting, treatment with pembrolizumab appears to be a viable option for patients with metastatic uveal melanoma [42].

Prognostic and predictive factors

The identification of prognostic factors is of limited value due to the lack of effective treatment to prevent or delay metastasis, or for metastatic disease itself. The patients treated with plaque brachytherapy, proton beam radiotherapy or stereotactic radiotherapy should be monitored for tumor regression intensively over the first two years following treatment [43]. Further follow up is decided on the basis of response of the tumor to brachytherapy and the radiotherapy complications experienced.

Clinical prognostic factors

Anatomic site

Ciliary body melanoma has the poorest prognosis as compared to choroidal or iris melanoma. Tumors actually arising in the ciliary body are aggressive and have a 5-year mortality of 53%, compared with 14% for choroidal-based melanomas [43]. Invasion of the optic nerve worsens the prognosis [44]. If a tumor extends outside the eye, the 10-year mortality rate is 75%.

Tumor growth pattern

About 5% of posterior uveal melanomas grow in a diffuse pattern. Twenty-four percent of patients with diffuse melanoma have metastases at 5 years and 36% at 10 years [45].

Tumor size

Tumor size is extremely useful as tumor measurements are available at the time of diagnosis, thus it can help in prognostication of the patient [46].

Histopathological prognostic factors

Microvascular patterns

The presence of microvascular networks, defined as at least three back-to-back closed loops, is a feature strongly associated with the development of metastatic disease [43].

Cell type

Cell type, as determined by the Callender classification, is predictive of outcome. It was found that 95% of patients with spindle A tumors, 85% of those with spindle B tumors, 60% of those with mixed tumors, and 83% with epithelioid tumors were alive 5 years after enucleation [8].

Tumor-infiltrating lymphocytes and macrophages

Tumor-infiltrating macrophages (CD68+ cells) are an independent prognostic factor for survival [47]. Approximately 5–12% of uveal melanomas contain lymphocytes, and these are thought to represent an important component of the host's immune response to the tumor. Both T- and B-lymphocyte infiltrations were associated with higher mortality.

Cytogenetic and molecular prognostic factors

Uveal melanomas characterized by monosomy 3 have aggressive tumor behavior, such as greater tumor size, ciliary body involvement, the presence of epithelioid cells, and closed loop vasculogenic mimicry [48]. Conversely, metastasis in the absence of monosomy 3 is rare. Also important in uveal melanomas are abnormalities involving chromosomes 8, 6, 9, and 1 [49].

Rb protein is expressed in virtually all melanomas, indicating a lack of *Rb* gene mutation [49]. Gain of chromosome 8q correlates strongly with the expression of *DDEF1*, a gene located at 8q24. *DDEF1* may act as an oncogene in uveal melanoma, and it may be a useful diagnostic marker [50]. Also, the expression of the Nijmegen breakage syndrome (*NBS1*) gene was a strong predictor of uveal melanoma survival [49].

Surveillance options for patients with uveal melanoma following definitive management

About 50% of melanoma patients who have attained local control ultimately develop distant metastases. Still there is no consensus about the role of surveillance for the detection of metastatic disease in these patients. Since there is no survival benefit from the early detection of asymptomatic disease, there is controversy over the value of routine surveillance. Table 3 depicts the various modalities for the surveillance of uveal melanoma along with their advantages and disadvantages.

Conclusions

Uveal melanoma is a complex malignancy that requires a high degree of expertise in its management. To select the best possible strategy, the management plan should be individualized. Despite all measures, uveal melanoma has a high propensity for distant failure.

Conflicts of interest

Nil.

Source of funding

Nil.

References

[1] Singh AD, Bergman L, Seregard S. Uveal melanoma: epidemiological aspects. Ophthalmol Clin North Am 2005;18:75.
[2] Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earle JD, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: collaborative Ocular Melanoma Study Group Report No. 26. Arch Ophthalmol. 2005;123(12):1639–43.
[3] Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earle JD, et al. Screening for metastasis from choroidal melanoma: the Collaborative Ocular Melanoma Study Group Report 23. J Clin Oncol. 2004;22(12):2438–44.
[4] Singh AD, Topham A. Incidence of uveal melanoma in the United States: 1973–1997. Ophthalmology 2003;110(5):956–61.
[5] Weis E, Shah CP, Lajous M, Shields JA, Shields CL. The association between host susceptibility factors and uveal melanoma: a meta-analysis. Arch Ophthalmol 2006;124 (1):54–60.
[6] Satyanarayan, Nangal J, Kapoor A, Sharma N. Vaginal amelanotic nodular malignant melanoma in a middle-aged female: a rare case report and review of literature. J Obstet Gynaecol India 2015;65(3):199–201.
[7] Lee DS, Anderson SF, Perez EM, Townsend JC. Amelanotic choroidal nevus and melanoma: cytology, tumor size, and pigmentation as prognostic indicators. Optom Vis Sci 2001;78 (7):483–91.
[8] McLean IW, Foster WD, Zimmerman LE, Gamel JW. Modifications of Callender's classification of uveal melanoma at the Armed Forces Institute of Pathology. Am J Ophthalmol 1983;96(4):502–9.
[9] Collaborative Ocular Melanoma Study Group. Comparison of clinical, echographic, and histopathological measurements from eyes with medium-sized choroidal melanomas in the Collaborative Ocular Melanoma Study: COMS report no. 21. Arch Ophthalmol 2003;121(8):1163–71.
[10] Faulkner-Jones BE, Foster WJ, Harbour JW, Smith ME, Dávila RM. Fine needle aspiration biopsy with adjunct immunohistochemistry in intraocular tumor management. Acta Cytol 2005;49(3):297–308.
[11] Kvanta A, Seregard S, Kopp ED, All-Ericsson C, Landau I, Berglin L. Choroidal biopsies for intraocular tumors of indeterminate origin. Am J Ophthalmol 2005;140(6):1002–6.
[12] Daftari I, Aghaian E, O'Brien JM, Dillon W, Phillips TL. 3D MRI-based tumor delineation of ocular melanoma and its comparison with conventional techniques. Med Phys 2005;32 (11):3355–62.
[13] Shields CL, Shields JA. Recent developments in the management of choroidal melanoma. Curr Opin Ophthalmol 2004;15(3):244–51.
[14] Singh P, Singh A. Choroidal melanoma. Oman J Ophthalmol 2012;5(1):3–9.

[15] Atmaca LS, Batioğlu F, Atmaca P. Fluorescein and indocyanine green videoangiography of choroidal melanomas. Jpn J Ophthalmol 1999;43(1):25–30.
[16] Collaborative Ocular Melanoma Study Group. Accuracy of diagnosis of choroidal melanoma in the Collaborative Ocular Melanoma Study. COMS report No. 1. Arch Ophthalmol 1990;108(9):1268–73.
[17] Kurli M, Reddy S, Tena LB, Pavlick AC, Finger PT. Whole body positron emission tomography/computed tomography staging of metastatic choroidal melanoma. Am J Ophthalmol 2005;140(2):193–9.
[18] Keilholz U, Goldin-Lang P, Bechrakis NE, Max N, Letsch A, Schmittel A, et al. Quantitative detection of circulating tumor cells in cutaneous and ocular melanoma and quality assessment by real-time reverse transcriptase-polymerase chain reaction. Clin Cancer Res 2004;10(5):1605–12.
[19] Schuster R, Bechrakis NE, Stroux A, Busse A, Schmittel A, Scheibenbogen C, et al. Circulating tumor cells as prognostic factor for distant metastases and survival in patients with primary uveal melanoma. Clin Cancer Res 2007;13(4):1171–8.
[20] Mortality in patients with small choroidal melanoma. COMS report no. 4. The Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 1997;115(7):886–93.
[21] Malignant melanoma of the uvea staging form. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. p. 555.
[22] Shields CL, Shields JA, Perez N, Singh AD, Cater J. Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations. Ophthalmology 2002;109(2):225–34.
[23] Shields CL, Cater J, Shields JA, Chao A, Krema H, Materin M, et al. Combined plaque radiotherapy and transpupillary thermotherapy for choroidal melanoma: tumor control and treatment complications in 270 consecutive patients. Arch Ophthalmol 2002;120(7):933–40.
[24] Qiang Z, Cairns JD. Laser photocoagulation treatment of choroidal melanoma. Aust N Z J Ophthalmol 1993;21(2):87–92.
[25] Peyman GA, Apple DJ. Local excision of a choroidal malignant melanoma: full-thickness eyewall resection. Arch Ophthalmol 1974;92:216–8.
[26] Foulds WS, Damato BE. Alternatives to enucleation in the management of choroidal melanoma. Aust N Z J Ophthalmol 1986;14(1):19–27.
[27] Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. Ophthalmology 1999;106(8):1579–87.
[28] Char DH, Kroll SM, Castro J. Ten-year follow-up of helium ion therapy for uveal melanoma. Am J Ophthalmol 1998;125 (1):81–9.
[29] Gragoudas ES, Lane AM, Munzenrider A, Egan KM, Li W. Long-term risk of local failure after proton therapy for choroidal/ciliary body melanoma. Trans Am Ophthalmol Soc 2002;100:43–8, discussion 48-9.
[30] Daftari I, Petti PL, Shrieve DC, Phillips TL. Newer radiation modalities for choroidal tumors. Int Ophthalmol Clin 2006;46 (1):69–79.
[31] Diener-West M, Earle J, Fine SL, Hawkins BS, Moy CS, Reynolds SM, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma. III: initial mortality findings. COMS report no. 18. Arch Ophthalmol 2001;119 (7):969–82.
[32] Melia M, Abramson DH, Albert DM, Boldt HC, Earle JD, Hanson WF, et al. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16. Ophthalmology 2001;108(2):348–66.
[33] Finger PT, Berson A, Ng T, Szechter A. Palladium-103 plaque radiotherapy for choroidal melanoma: an 11-year study. Int J Radiat Oncol Biol Phys 2002;54(5):1438–45.
[34] Sobrin L, Schiffman JC, Markoe AM, Murray TG. Outcomes of iodine 125 plaque radiotherapy after initial observation of suspected small choroidal melanomas: a pilot study. Ophthalmology 2005;112(10):1777–83.
[35] Lumbroso L, Desjardins L, Levy C, Plancher C, Frau E, D'Hermies F, et al. Intraocular inflammation after proton beam irradiation for uveal melanoma. Br J Ophthalmol 2001;85 (11):1305–8.
[36] Shields CL, Shields JA, Suvarnamani C, Tantisira M, Shah P. Orbital exenteration with eyelid sparing: indications, technique, and results. Ophthalmic Surg 1991;22(5):292–7.
[37] Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma. II: initial mortality findings. COMS report no. 10. Am J Ophthalmol 1998;125(6):779–96.
[38] Buzzacco DM, Abdel-Rahman MH, Park S, Davidorf F, Olencki T, Cebulla CM. Long-term survivors with metastatic uveal melanoma. Open Ophthalmol J 2012;6:49–53.
[39] Kapoor A, Rungta A, Kumar HS, Kumar R. Combination immunotherapy in management of advanced melanoma. Clin Cancer Invest J 2014;3:361–2.
[40] Carvajal R. Another option in our KIT of effective therapies for advanced melanoma. J Clin Oncol 2013;31(26):3173–5.
[41] Bagri PK, Samdariya S, Pareek P, Rizwan Z. Targeting the programmed cell death 1 pathway: a new approach to the treatment of advanced melanoma. Clin Cancer Invest J 2015;4:290–1.
[42] Kottschade LA, McWilliams RR, Markovic S, Block MS, Bisneto JV, Pham AQ, et al. The use of pembrolizumab for the treatment of metastatic uveal melanoma. J Clin Invest 2015;33 (15-Suppl.):9010.
[43] Seddon JM, Albert DM, Lavin PT, Robinson N. A prognostic factor study of disease-free interval and survival following enucleation for uveal melanoma. Arch Ophthalmol 1983;101 (12):1894–9.
[44] Lindegaard J, Isager P, Prause JU, Heegaard S. Optic nerve invasion of uveal melanoma: clinical characteristics and metastatic pattern. Invest Ophthalmol Vis Sci 2006;47 (8):3268–75.
[45] Shields CL, Shields JA, De Potter P, Cater J, Tardio D, Barrett J. Diffuse choroidal melanoma. Clinical features predictive of metastasis. Arch Ophthalmol 1996;114(8):956–63.
[46] Kaiserman I, Anteby I, Chowers I, Blumenthal EZ, Kliers I, Pe'er J. Post-brachytherapy initial tumor regression rate correlates with metastatic spread in posterior uveal melanoma. Br J Ophthalmol 2004;88(7):892–5.
[47] Makitie T, Summanen P, Tarkkanen A, Kivelä T. Tumor-infiltrating macrophages (CD68(+) cells) and prognosis in malignant uveal melanoma. Invest Ophthalmol Vis Sci 2001;42 (7):1414–21.
[48] Prescher G, Bornfeld N, Hirche H, Horsthemke B, Jöckel KH, Becher R. Prognostic implications of monosomy 3 in uveal melanoma. Lancet 1996;347(9010):1222–5.
[49] Singh AD, Damato B, Howard P, Harbour JW. Uveal melanoma: genetic aspects. Ophthalmol Clin North Am 2005;18(1):85–97, viii.
[50] Ehlers JP, Worley L, Onken MD, Harbour JW. DDEF1 is located in an amplified region of chromosome 8q and is overexpressed in uveal melanoma. Clin Cancer Res 2005;11 (10):3609–13.